REMARKS

In the application, Claims 1- 24 are pending in view of the Examiner's decision to withdraw the restriction requirement and rejoin the claims of Group I and Group II. All claims are rejected. In view of the Examiner's comments, the claims have been amended a set forth above. Applicants now request reconsideration of the application as amended.

Objections

The Examiner has objected to Claim 23 based on a formality. In response, Applicants have amended the claim to modify the language identified in the objection.

35 USC § 101

The Examiner has rejected Claims 21-24 under 35 U.S.C. § 101 as being directed to non-statutory subject matter.

In response, claim 21 has been amended to specify in the preamble that the method is for controlling gene expression, which ties in with generation of "an output upon binding corresponding to a desired gene expression" in the last line of the claim. It is respectfully submitted that a method for controlling gene expression and generating an output corresponding to desired gene expression is not merely an abstract concept, but involves a physical transformation with regard to gene expression. Accordingly, it is requested that the Examiner withdraw this rejection.

35 USC § 112

The Examiner has rejected Claims 1-20 and 23 under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

In claim 1, the Examiner identifies the term "long-distance interactions" as indefinite. In response, the definition has been added into the claim to specify that a long-distance interaction is one which avoids inference between DNA binding sites. As described in the specification at paragraphs [0061] - [0064], promoter overcrowding can be a problem, particularly with complex logical functions. Long-distance interactions are described as the solution to overcrowding.

Accordingly, a long-distance interaction is one in which the interference that arises from overcrowding is avoided.

Claims 1, 2 and 8 have been amended to provide proper antecedent basis for two or more cis-regulatory regions, and claim 11 has been amended for consistent usage of one or more cis-regulatory regions.

In claims 6 and 16, "effective" has been deleted and "generic" has been changed to "glue-like". Addressing the Examiner's comments about "glue-like", the specification at paragraph [0009] defines "glue-like" interactions as interactions which do not require specific contacts to induce allosteric transitions.

Paragraph [0009] of the specification provides the following description:

Regulated recruitment refers to a situation where TFs regulate transcription simply by "recruiting", i.e., attracting, RNA polymerase to the promoter sequences on the DNA. This mechanism involves only simple and generic, "glue-like" protein-protein interactions, in contrast to other known mechanisms of activation which require specific contacts to induce allosteric transitions in the conformation of the molecules. (Emph. added.)

See also paragraph [0031], which again describes the protein-protein interactions as lacking allosteric effects:

Protein-DNA binding : A simple modular structure can be assumed for the TFs with several distinct functional domains for DNA-binding and protein-protein interactions (Frankel and Kim 1991). Interactions among the TFs, the DNA, and the RNA polymerase are treated as simple pairwise interactions, not invoking any allosteric effects (apart from possible TF activation by ligand binding).

"Regulated recruitment" mentioned in paragraph [0009] is described in numerous books and journal articles including the references by Ptashne and Gann and others identified in, and incorporated by reference into, the specification. Excerpts describing "glue-like" interactions taken from two of the cited references are provided below:

"Each of the protein-protein and protein-DNA interactions encountered in this example involves a patch on the surface of the relevant molecule that we might characterize as "glue-like." This term accurately conveys the image of simple binding (adhesive) interactions. But the interactions are often highly specific and they span a broad range of affinities."
From *Genes & Signals*, Mark Ptashne, Alexander Gann, Cold Spring Harbor Laboratory Press, 2002, p. 26.

"In the simplest scenario, neither partner of a pair of cooperatively binding proteins needs to undergo a modification or a conformational change, rather, the interaction between the proteins, as

well as that between the proteins and DNA, need only provide binding energy. Therefore, these kinds of interactions - which can of course be highly specific - need only be adhesive (glue- or velcro-like)."
From "Imposing specificity by localization: mechanism and evolvability", Mark Ptashne, Alexander Gann, *Current Biology*, Volume 8, Issue 24, 3 December 1998, Pages R896-R897.

It is respectfully submitted that the specification, especially when combined with the information contained in cited references that were incorporated by reference, provides a definition of the term "glue-like" that makes it sufficiently definite to a person of skill in the art such that the subject matter of the claimed invention is clear.

It is believed that all issues raised by the Examiner in the rejections under §112 have been addressed and overcome. Accordingly, the Examiner is requested to withdraw the rejections under this section.

35 USC § 102

The Examiner has rejected claim 21 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,814,618 of Bujard et al. (hereinafter "Bujard et al.").

Claim 21 has been amended to include additional limitations of one or more regulatory DNA sequences to exert combinatorial control of gene expression to operate as at least one logic function of a plurality of different logic functions for generating an output corresponding to a desired gene expression upon binding of two or more regulatory proteins, wherein each different logic function corresponds to a different gene expression.

It is respectfully submitted that Bujard et al. teach binding of a single fusion protein that has two distinct polypeptides, which is different from binding of two or more regulatory proteins as claimed.

Most regulatory proteins, or transcription factors, have multiple "domains", which are parts of proteins that do different things. One of these domains is the "DNA binding domain", which is the part responsible for the binding of the regulatory protein with the DNA. Another domain is the activation domain, which is responsible for mediating the "glue-like" interaction between the regulatory protein and the RNA polymerase (the latter being the machinery that must be launched to start transcription.) Bujard et al's patent discloses mixing the different interaction domains together with the DNA binding domain of a specific regulator (TetR). The "AND" operation to which the

Examiner refers is that both the DNA binding and interaction are needed for this chimeric protein to function, however, it still represents only a single input. Bujard et al. do not disclose binding of two or more regulatory proteins and, therefore, are unable to exert combinatorial control of gene expression as would truly be needed to construct logic functions.

In view of the claim amendments, important elements of the claim are not disclosed by Bujard et al. and, as such, the Bujard et al. patent cannot anticipate the invention as now claimed. Accordingly, the Examiner is respectfully requested to withdraw the rejection under § 102.

35 USC §103

The Examiner has rejected Claims 1, 3, 5, 7-8, 11, 13, 15, and 17-18 under 35 U.S.C. §103(a) as being unpatentable over Bujard et al. in view of Kirch et al. in view of Orkin.

The Examiner asserts that Bujard et al. teach implementation of a logic function, particularly an AND operation, using two distinct regulatory proteins. Furthermore, the Examiner states that Bujard, et al. teach adjustment of the binding strength and location of the peptides. However, as stated above, the chimeric protein described by Bujard et al. actually functions as a single regulatory protein, and, therefore, would be incapable of combinatorial transcription control.

Claims 1 and 11 have been amended to include the steps of identifying a plurality of logic functions, each logic function having an output corresponding to a different gene output signal; and selecting at least one logic function corresponding to a desired target gene output signal. Ignoring the fact that Bujard et al. actually only teach a single regulatory protein, if one were to look at the need for two separate peptides, this might in some sense be an AND operation. However, that a logic operation is performed at all is mere chance -- two separate conditions are required to be present (DNA binding and interaction) for the desired function to occur, which makes it like an AND operation. However, nothing in Bujard et al. teaches or suggests that a plurality of different logic functions can be executed by combinatorially controlling transcription using interactions between two or more regulatory proteins and DNA binding sites of cis-regulatory regions, where the binding strengths and locations are adjustable.

To provide a simple illustration, in order for an automobile collision to occur, there must be both a failure to stop the car and an obstacle in the car's path with which it could collide. The fact that this may be logical does not make it a "logic function," which is "an elementary processing

function in a digital circuit" (from pcmag.com encyclopedia). "Logic design involves determining how to interconnect basic logic building blocks to perform a specific function" in a digital system. (p.5, Charles H. Roth, Jr., *Fundamentals of Logic Design*, Second Edition, 1979, West Publishing Co.). Also relevant is the term "combinatorial logic", which refers to a digital logic function in which the outputs of the functions are directly related to the present value of the inputs. (*Id.*)

An important object of the invention is to create a genetic computing scheme that involves the creation of a digital system for performing combinatorial logic by controlling gene expression using logic functions. A single logic function is not a computing scheme -- multiple logic functions are required. The independent claims as amended specify that multiple different logic functions may be created.

The Examiner cites the Kirch et al. article as teaching synergistic activation of transcription from the p53 promoter via three different motifs, and particularly points to the mutation of sequence composition at one of the loci to adjust transcription.

While it appears that Kirch et al. would teach an AND-like function as a result of the requirement of the combination of different motifs, there is still nothing to suggest that multiple different logic functions could be implemented by various combinations of two or more regulatory proteins and adjustment of binding strengths and locations in cis-regulatory regions. Kirch et al. present a case similar to that of Bujard et al. -- the fact that multiple conditions must be present would effectively provide an AND-like operation, but there is no intention to perform a logic operation for creating a digital system (a genetic computer), and no suggestion that other logic operations could be performed by different combinations of the multiple conditions. Accordingly, Kirch et al. does not bring to a combination with Bujard et al. what is missing from Bujard et al. As such, the combination does not teach or suggest Applicants' invention as now claimed.

The Examiner relies on Orkin for its disclosure of protein-protein interactions in regulating transcription control. However, Orkin does not teach or suggest a plurality of logic functions that can be implemented by various combinations of two or more regulatory proteins and adjustment of binding strengths and locations in cis-regulatory regions.

Accordingly, the combination of Bujard et al., Kirch et al. and Orkin fails to teach or suggest a method of combinatorially controlling transcription by implementing one of a plurality of

different logic functions as claimed, and the Examiner is respectfully requested to withdraw the rejection under §103.

The Examiner has also rejected claims 2 and 12 under 35 U.S.C. § 103(2) as being unpatentable over Bujard et al. in view of Kirch et al. in view of Orkin as applied above, and further in view of Kirchhamer et al.

Kirchhamer et al. are cited for their disclosure of modular cis-regulatory organization, however, Kirchhamer et al. do not teach or suggest a method of combinatorially controlling transcription by implementing one of a plurality of different logic functions as claimed. As a result, combination of the teachings of Kirchhamer et al. with that of Bujard et al., Kirch et al. and Orkin does not render the claimed methods obvious.

The Examiner has also rejected claims 4, 6, 14, and 16 under 35 U.S.C. § 103(a) as being unpatentable over Bujard et al. in view of Kirch et al. in view of Orkin as applied to Claims 1, 3, 5, 7-8, 11, 13, 15 and 17-17, and further in view of Renkawitz.

The Renkawitz article is cited for its disclosure of transcription repression, however, Renkawitz does not teach or suggest a method of combinatorially controlling transcription by implementing one of a plurality of different logic functions as claimed. As a result, combination of the teachings of Renkawitz with that of Bujard et al., Kirch et al. and Orkin does not render the claimed methods obvious.

The Examiner has also rejected claims 9 and 19 under 35 U.S.C. § 103(a) as being unpatentable over Bujard et al. in view of Kirch et al. in view of Orkin as applied to Claims 1, 3, 5, 7-8, 11, 13, 15 and 17-18, and further in view of U.S. Patent No. 5,535,382 issued July 9, 1996 to Ogawa (hereinafter Ogawa).

Ogawa is cited for its disclosure of the use of logic functions in minimal conjunctive normal form for ranking the results of a document retrieval system. It is respectfully submitted that, Ogawa not teach or suggest a method of combinatorially controlling transcription by implementing one of a plurality of different logic functions as claimed. Furthermore, as there is nothing in either Bujard et al., Kirch et al. and Orkin, alone or in combination, that provides any suggestion of attempting to implement a plurality of different logic functions for controlling transcription. As such, there would have been no motivation to combine the teachings of Ogawa relative to a document retrieval system with any of Bujard et al., Kirch et al. and Orkin.

While the Examiner may attempt to suggest that *KSR v. Teleflex* (550 U.S. ___, 127 S. Ct. 1727 (2007)) has dispensed with the "lack of motivation" argument against an obviousness rejection, it must be kept in mind that there is a significant difference between asserting "common sense" when combining two references relating to gas pedal designs and two references in entirely different areas of science such as electronic document retrieval and gene expression control. Nothing in the gene expression references relied on by the Examiner has anything to do with computing, so there would be absolutely no motivation to look to the document retrieval art to utilize logic techniques in combination with gene expression control.

The Examiner has also rejected claims 10 and 20 under 35 U.S.C. § 103(a) as being unpatentable over Bujard et al. in view of Kirch et al. in view of Orkin in view of Ogawa as applied to claims 1, 3, 5, 7-8, 11, 13, 15 and 17-18, and further in view of Gardner et al.

For the reasons set forth in the preceding discussion, the combination of Bujard et al., Kirch et al. and Orkin with Ogawa does not render the claimed invention obvious, and, therefore, are patentable over the prior art. The combination of the three references with Gardner et al., which teach a genetic switch, still fails to teach or suggest the implementation of a plurality of different logic functions by combinatorial control of transcription. A switch is either on or off; it does not perform logic functions, nor does it teach how to control transcription by combining two or more regulatory proteins with a cis-regulatory region that has adjustable binding strengths and sites.

The Examiner has also rejected claim 22 under 35 U.S.C. § 103(a) as being unpatentable over Bujard et al. as applied to claim 21, and further in view of Kirchhamer et al.

The Examiner asserts that Bujard et al. teach implementation of a logic function, particularly an AND operation, using two distinct regulatory proteins. Furthermore, the Examiner states that Bujard, et al. teach adjustment of the binding strength and location of the peptides. However, as stated above, the chimeric protein described by Bujard et al. actually functions as a single regulatory protein, and, therefore, would be incapable of combinatorial transcription control.

Kirchhamer et al. are cited for their disclosure of modular cis-regulatory organization, however, Kirchhamer et al. do not teach or suggest a method of combinatorially controlling transcription by implementing one of a plurality of different logic functions as claimed. As a result, combination of the teachings of Kirchhamer et al. with that of Bujard et al., does not render the claimed methods obvious.

The Examiner has also rejected claims 23-24 under 35 U.S.C. § 103(a) as being unpatentable over Bujard et al. as applied to claim 21, and further in view of Orkin.

The Examiner relies on Orkin for its disclosure of protein-protein interactions in regulating transcription control. However, Orkin does not teach or suggest a plurality of logic functions that can be implemented by various combinations of two or more regulatory proteins and adjustment of binding strengths and locations in cis-regulatory regions.

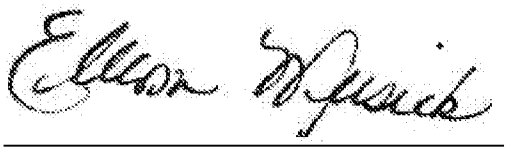
Because Bujard et al. do not disclose a method for combinatorial control of transcription using logic functions, it is respectfully submitted that the invention as claimed would not be obvious to one of skill in the art because none of the secondary references disclose what is missing from Bujard et al. Accordingly, the Examiner is respectfully requested to withdraw all rejections under §103.

Conclusion

It is believed that all grounds for rejection have been addressed and overcome. The Examiner is respectfully requested to reconsider the claims as amended, withdraw the objections and rejections, and issue a notice of allowance of all claims now pending in the application.

Should the Examiner believe that prosecution of this application might be expedited by further discussion of the issues, he is invited to telephone the undersigned attorney for Applicants at the telephone number indicated below.

Respectfully submitted,



Dated: October 10, 2008 By: _____

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